

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/086275 A2

(51) International Patent Classification⁷: A61K

(21) International Application Number: PCT/IN03/00156

(22) International Filing Date: 16 April 2003 (16.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
348/MUM/2002 15 April 2002 (15.04.2002) IN

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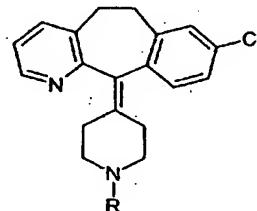
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

[Continued on next page]

(54) Title: SUBSTANTIALLY PURE ANTIHISTAMINIC COMPOUND



(3)

WO 03/086275 A2

(57) Abstract: The present invention provides substantially pure desloratadine having an HPLC purity greater than 99.5% and having an absorbance less than 0.15 Au at 420 nm for a 5%w/v solution in methanol, which does not show a peak for an impurity at a relative retention time in the range from about 0.85 to about 0.99 (relative to desloratadine appearing at a retention time of 25±5 minutes), which is greater than the discard limit set at less than 0.025% of the total area, when tested according to an HPLC method performed using a Hypersil BDS C₈ column (15cm x 4.6mm, 5 μm particle size) with the following parameters: Mobile phase: Buffer solution having a pH of about 3, methanol and acetonitrile in a volume ratio of 8:1:1; Injection volume: 20μl; Flow rate: 1.5 ml/minute; Run time: 75 minutes; Discard limit: Set at less than 0.025% of total area. The present invention also provides a process for the preparation of substantially pure desloratadine by the process comprising acidic hydrolysis of a compound of formula (3) where R is selected from COR₁, COOR₁ wherein R₁ is selected from branched or linear alkyl (1-6 C), cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and their substituted analogs; and their substituted analogs with a strong organic acid or a mineral acid.



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Published:

— without international search report and to be republished upon receipt of that report

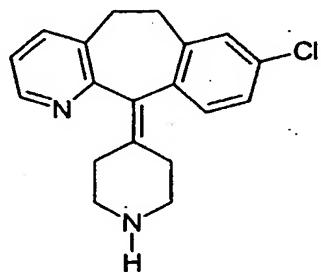
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SUBSTANTIALLY PURE ANTIHISTAMINIC COMPOUND**FIELD OF THE INVENTION:**

5

The present invention relates to substantially pure desloratadine, a compound of formula 1, and a process of preparation thereof. Desloratadine, 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, is an antihistaminic agent useful in the treatment of seasonal allergic rhinitis.

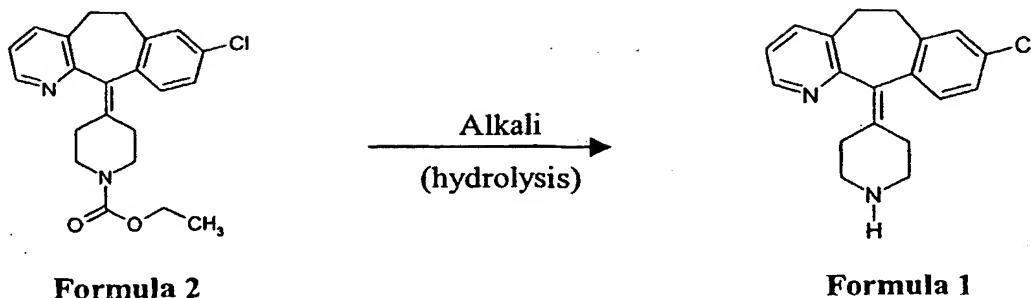
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**Formula 1****BACKGROUND OF THE INVENTION:**

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The PCT publication WO 8503707 (hereinafter referred to as the '707 application, equivalent of which is the United States Patent No. 4,659,716) claims desloratadine and exemplifies the process of its preparation by alkaline hydrolysis of loratadine (formula 2, scheme 1), followed by treatment with acetic acid to give the acetate salt of desloratadine, and then converting the acetate into the free base of desloratadine. 20 However, the '707 application does not disclose the purity levels of desloratadine or its impurity profile.

Scheme 1



The PCT publication WO 9901450 (equivalent of which is the United States Patent No. 6,506,767) discloses the polymorphic forms 1 and 2 of desloratadine. Preparation of the polymorphic forms 1 and 2 is disclosed by employing alkaline hydrolysis of loratadine by a process similar to that described in the '707 application, and then crystallization from methyl isobutyl ketone, hexanol, methanol, 3-methyl-1-butanol, cyclohexanol, chlorinated solvents such as dichloromethane, ethyl acetate and ether solvents such as dioxane, di-isopropylether, di-n-butylether. However, WO 9901450 too does not disclose the purity levels of desloratadine or its impurity profile.

The PCT application WO 02/42290 claims acid addition salts of desloratadine namely, monoacid, hemiacid and diacid salts. It discloses a process for preparation of diacid salts by reacting loratadine with concentrated mineral acids. It also teaches a process for conversion of diacid salts to monoacid or hemiacid salts by treatment with a solution of a base. It provides new desloratadine hemisulfate salt which is prepared from desloratadine disulfate salt with High Performance Liquid Chromatography (referred to as HPLC herein) purity greater than 99.5% by treatment with a solution of aqueous ammonia.

20

We have found that desloratadine when prepared according to the prior art processes shows a HPLC peak for an impurity at a relative retention time in the range from about 0.85 to about 0.99 (with respect to desloratadine), which is greater than the discard limit set at less than 0.025% of the total area, when tested according to an HPLC method

performed using a Hypersil BDS C₈ column (15 cm x 4.6 mm, 5 µm particle size) with the following parameters:

Mobile phase : Buffer solution having a pH of about 3, methanol and acetonitrile in a volume ratio of 8:1:1.

5 Injection volume : 20µl

Flow rate : 1.5 ml/min

Run time : 75 mins.

Discard limit : Set at less than 0.025% of total area

10 **OBJECTS OF THE INVENTION:**

The object of the present invention is to provide substantially pure desloratadine and a process for preparation thereof.

15 A specific object of the present invention is to provide substantially pure desloratadine having an HPLC purity greater than 99.5%, and having an absorbance less than 0.15 Au at 420 nm for a 5%w/v solution in methanol.

20 A more specific object of the present invention is to provide substantially pure desloratadine which does not show a peak for an impurity at a relative retention time in the range from about 0.85 to about 0.99 (relative to desloratadine appearing at a retention time of 25 ± 5 minutes), which is greater than the discard limit set at less than 0.025% of the total area, when tested according to an HPLC method performed using a Hypersil BDS C₈ column (15cm x 4.6mm, 5 µm particle size) with the following

25 parameters:

Mobile phase : Buffer solution having a pH of about 3, methanol and acetonitrile in a volume ratio of 8:1:1.

Injection volume : 20µl

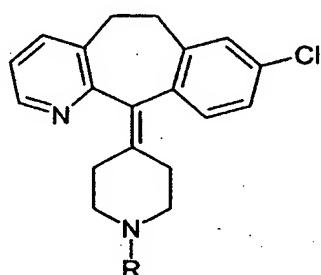
Flow rate : 1.5 ml/minute

30 Run time : 75 minutes

Discard limit : Set at less than 0.025% of total area

More specifically, the object is to provide substantially pure desloratadine devoid or almost free of the said impurity and with total impurities less than 0.5%, preferably less than 0.3%, and no individual impurity greater than 0.1% and having UV absorbance less than 0.15 Au, preferably less than 0.10 Au at 420 nm for a 5%w/v solution in methanol.

Another object of the present invention is to provide a process for the preparation of substantially pure desloratadine which comprises acidic hydrolysis of a compound of formula 3 where R is selected from COR₁, COOR₁ wherein R₁ is selected from branched or linear alkyl (1-6 C), cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and their substituted analogs; and their substituted analogs with a strong organic acid or a mineral acid.



Formula 3

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DETAILED DESCRIPTION OF THE PRESENT INVENTION:

The present invention provides substantially pure desloratadine and a process for preparation thereof.

The substantially pure desloratadine of the present invention has an HPLC purity greater than 99.5% and having an absorbance less than 0.15 Au at 420 nm for a 5%w/v solution in methanol.

25

Substantially pure desloratadine of the present invention does not show a peak for an impurity at a relative retention time in the range from about 0.85 to about 0.99 (relative to desloratadine appearing at a retention time of 25+5 minutes), which is greater than the discard limit set at less than 0.025% of total area, when tested according to an HPLC 5 method performed using a Hypersil BDS C₈ column (15cm x 4.6mm, 5 µm particle size) with the following parameters:

Mobile phase : Buffer solution having a pH of about 3, methanol and acetonitrile in a volume ratio of 8:1:1.

10 Injection volume : 20µl

Flow rate : 1.5 ml/minute

Run time : 75 minutes

Discard limit : Set at less than 0.025% of total area

15 Relative retention time as referred to herein is the ratio of the retention time of the impurity to the retention time of desloratadine.

In preferred embodiment, the substantially pure desloratadine of the present invention is such that (a) total impurities are less than 0.5%; and (b) individual impurity is less than 0.1%.

20 Preferably substantially pure desloratadine according to the present invention is such that total impurities are not more than 0.3%, and has an absorbance less than 0.10 Au at 420 nm for a 5%w/v solution in methanol.

25 More preferably substantially pure desloratadine according to the present invention is such that total impurities are not more than 0.3%.

In the present invention substantially pure desloratadine when tested according to an HPLC method performed using a Hypersil BDS C₈ column (15cm x 4.6mm, 5 µm 30 particle size) with the following parameters:

Mobile phase : Buffer solution having a pH of about 3, methanol and acetonitrile in a volume ratio of 8:1:1.

Injection volume : 20 μ l

Flow rate : 1.5 ml/minute

5 Run time : 75 minutes

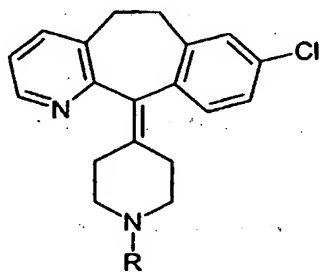
Discard limit : Set at less than 0.025% of total area

is characterized by a peak at 25+5 minutes and does not show a peak for an impurity at a relative retention time in the range from about 0.85 to about 0.99 (with respect to desloratadine), which is greater than the discard limit set at less than 0.025% of the total area.

The present invention also provides a process for the preparation of substantially pure desloratadine.

15 The present invention provides a process for preparation of the substantially pure desloratadine comprising acidic hydrolysis of a compound of formula 3 where R is selected from COR₁, COOR₁ wherein R₁ is selected from branched or linear alkyl (1-6 C), cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and their substituted analogs; and their substituted analogs with a strong organic acid or a mineral acid.

20



Formula 3

25

The substantially pure desloratadine may be prepared by acidic hydrolysis of a compound of formula 3 by heating with a strong organic acid or a mineral acid for a period of about 1 hour to about 24 hours. The temperature of reaction may vary from ambient to 150° C, preferably between about 60° C to about 110° C. Examples of the 5 organic acids include aqueous substituted and unsubstituted (C1 to C3) alkylsulfonic acids such as methanesulfonic acid, ethanesulfonic acid, halomethanesulfonic acids such as trifluoromethane sulfonic acid, fluoromethanesulfonic acid, chloromethanesulfonic acid, dichloromethanesulfonic acid, trichloromethane sulfonic acid and the like; substituted and unsubstituted aqueous arylsulfonic acids such as benzenesulfonic acid, 10 para-toluenesulfonic acid, 4-chlorobenzenesulfonic acid and the like. Preferred organic acid is aqueous methanesulfonic acid, more preferably 90 % methanesulfonic acid or greater than 90%. Examples of mineral acids include aqueous mineral acid such as halogen acids, phosphoric acid, polyphosphoric acid, perchloric acid, sulfuric acid and the like. The preferred mineral acid is aqueous sulfuric acid.

15

The hydrolysed reaction mixture is subjected to adjustment of pH between the range of about 3 to about 5, optional treatment with an adsorbent, adjustment of pH of the reaction mixture to a pH of about greater than 9 and isolation of desloratadine, for example by extraction with an organic solvent. The adsorbent is selected from charcoal, 20 neutral or alkaline alumina, silica, fuller's earth and the like.

In a preferred embodiment the hydrolysed reaction mixture is subjected to adjustment of pH between the range of about 4 to about 5, optional treatment with charcoal, adjustment of pH of the reaction mixture to a pH of greater than about 9, preferably greater than 25 about 9.5; and isolation of desloratadine, for example by extraction with an organic solvent.

The acidic hydrolysis process of the present invention may be carried out by heating with an acid for 1 about hour to about 24 hours at a temperature between the range of 30 ambient to about 150°C, preferably between the range of about 60°C to about 110°C.

In a preferred embodiment of the present invention, the compound of formula 3 is the one wherein R is COOR₁ and R₁ is ethyl i.e. the compound of formula 3 is 8-chloro-11-(1-carbonylethoxy-piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta [1,2-b] pyridine, and the organic acid used for acidic hydrolysis is methanesulfonic acid. The 5 acidic hydrolysis reaction with methanesulfonic acid is preferably carried out for about 5 to about 15 hours at a temperature between the range of about 90°C to about 120°C.

In another preferred embodiment of the present invention, the compound of formula 3 is the one wherein R is COOR₁ and R₁ is ethyl i.e. the compound of formula 3 is 8-chloro-11-(1-carbonylethoxy-piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta [1,2-b] pyridine, and the mineral acid used for acidic hydrolysis is sulphuric acid. The acidic hydrolysis reaction with sulphuric acid is preferably carried out for about 1 to about 5 hours at a temperature between the range of about 90°C to about 120°C.

15 The desloratadine prepared by the process of the present invention may be further purified by recrystallization by dissolving desloratadine in a solvent mixture comprising two or more solvents, concentrating, cooling and isolating the substantially pure desloratadine by conventional means. The solvent system used in this step may comprise of two or more solvents selected from protic or aprotic solvents selected from water, 20 alcohols, linear branched or cyclic hydrocarbons, aromatic hydrocarbons, ethers, ketones, nitriles, esters, and their halo or substituted analogs and the like, preferably the solvent system comprises a mixture of an alcohol like methanol and a hydrocarbon solvent like cyclohexane, more preferably the ratio of methanol:cyclohexane is 1:14 v/v.

25

The invention is further illustrated but not restricted by the description in the following examples.

30

EXAMPLES**Example 1**

5 A mixture of 4-(8-chloro-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylic acid ethyl ester (loratadine) (100.0 g, 0.26 mol), and 50% aqueous sulfuric acid (300 ml) was heated to 100-105° C for 3 hrs. The reaction mass was cooled to ambient temperature and quenched into ice cold water (300ml). The pH of the quenched mass was adjusted to pH 4.0 to 5.0 with liquor ammonia and 10 charcoalized (5g decolorizing charcoal). The pH of the charcoalized solution was adjusted to > 9.5 with liquor ammonia, and sticky semi-solid mass which separated was extracted into toluene (700ml). The toluene extract was concentrated under reduced pressure at below 65° C and degassed to obtain an off-white to white solid of desloratadine (yield 78.0 g, 96%, purity > 99.0%). HPLC analysis of the sample (as per 15 the procedure described in example 2) did not show any peak due to impurity at relative retention time of 0.85 to 0.99 (relative to desloratadine peak).

The product obtained as above was dissolved in cyclohexane-methanol mixture (14:1, 750ml) at 60-65° C, concentrated solution (to 550ml) at atmospheric pressure and then 20 cooled gradually to 10-15° C. Digested for 2 hrs at 10-15° C, filtered, and dried at 50-55° C to obtain 8-chloro-11-piperidin-4-ylidene-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (desloratadine) (73g , overall 90.0 % yield, purity 99.92 %. Absorbance at 420 nm for a 5%w/v solution in methanol is 0.032 Au).

Example 2**HPLC ANALYTICAL METHOD****Buffer :**

Transfer 15.2 g of triethylamine into a 1000 ml volumetric flask. Dissolve in and dilute 30 upto mark with HPLC grade water. Adjust the pH of the solution to 3.0 ± 0.1 with 85% orthophosphoric acid.

Mobile phase :

Mix buffer solution, methanol and acetonitrile in the ratio of 800 : 100 : 100. Filter and degas prior to use.

5 Sample preparation :

Transfer about 50 mg accurately weighed sample into a 50 ml volumetric flask. Dissolve in and dilute upto mark with mobile phase.

System suitability solution :

10 Transfer about 20 mg of desloratadine into a 100 ml volumetric flask. Dissolve in and dilute upto mark with mobile phase

Chromatographic system :

15 The liquid chromatograph is equipped with a 220 nm UV detector and 15 cm x 4.6 mm, 5 μ column that contains Hypersil BDS C8. The flow rate is about 1.5 ml/min.

Procedure:

20 Inject 20 μ l of system suitability solution into the system and record the chromatograms upto 75 min. Calculate the tailing factor of desloratadine peak. It should not be more than 2 and number of theoretical plates should not be less than 3000.

25 Inject 20 μ l of the sample preparation into the system and record the chromatogram upto 75 min. The retention time of desloratadine is 25 \pm 5 min. Calculate the amount of related substances by area normalization method, while disregarding any peak with an area percentage less than 0.025.

30 Desloratadine prepared according to the process of the present invention did not show a peak for an impurity at a relative retention time of 0.85 to 0.99 when tested according to the above method, however this impurity was found in desloratadine when prepared according to PCT publication Nos. WO 8503707 and WO 9901450.

Example 3**Loratadine hydrolysis by non-mineral acid**

5

A mixture of 4-(8-chloro-5,6-dihydrobenzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylic acid ethyl ester (loratadine) (50.0 g, 0.13 mol), and 90%v/v aqueous methanesulfonic acid (165ml) was heated to 105-110°C for 9 hrs. The reaction mass was cooled to ambient temperature, quenched into water (300ml) and the resulting solution heated at 90-100°C for 1 hour. The reaction mixture was cooled to ambient temperature and extracted once with toluene (100ml). The pH of the aqueous layer was adjusted between 4.0 to 5.0 with liquor ammonia and charcoalized (2.5g decolorizing charcoal). The pH of the charcoalized solution was adjusted to > 9.5 with liquor ammonia, and the sticky semi-solid mass which separated was extracted into toluene (300ml). The toluene extract was concentrated under reduced pressure at below 15 65°C and degassed to obtain an off-white to white solid of desloratadine (yield 40.5g, purity > 99.0%). HPLC analysis of the sample (as per the procedure described in example 2) did not show any peak due to impurity at relative retention time of 0.85 to 0.99 (relative to desloratadine peak).

20

The product obtained as above was purified from cyclohexane-methanol mixture (14:1, 750ml) as in example-1 to obtain 8-chloro-11-piperidin-4-ylidene-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (desloratadine) (36.14g, overall 89.0 % yield, purity 99.96 %. *Absorbance at 420 nm for a 5%w/v solution in methanol is 0.067 Au*).

25

Comparative example:

Tablet of Neoclarityn® (brand leader of desloratadine) containing 5 mg of desloratadine was crushed and powdered using pestle and mortar. The powder was taken up in 10 ml of the mobile phase (prepared as in example 2), sonicated for 10 mins. and filtered. HPLC chromatogram was recorded of this solution as per the procedure described in

example 2. The chromatogram showed desloratadine at a retention time of 24.33 minutes, and an impurity at a relative retention time of 0.91 amounting to 0.12%.

We claim

1. Substantially pure desloratadine having an HPLC purity greater than 99.5%, and
5 having an absorbance less than 0.15 Au at 420 nm for a 5%w/v solution in methanol,
which does not show a peak for an impurity at a relative retention time in the range
from about 0.85 to about 0.99 (relative to desloratadine appearing at a retention time
of 25 ± 5 minutes) which is greater than the discard limit set at less than 0.025% of
10 total area, when tested according to an HPLC method performed using a Hypersil
BDS C₈ column (15 cm x 4.6 mm, 5 μ m particle size) with the following parameters:
Mobile phase: Buffer solution having a pH of about 3, methanol and acetonitrile in a
volume ratio of 8:1:1.

Injection volume : 20 μ l

Flow rate : 1.5 ml/minute

15 Run time : 75 minutes

Discard limit : Set at less than 0.025% of total area

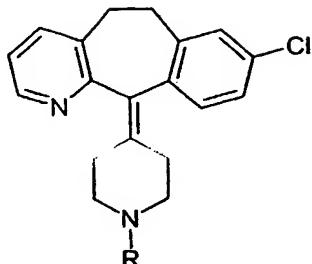
2. Substantially pure desloratadine as claimed in claim 1, wherein (a) total impurities
20 are not more than 0.5%; and (b) no individual impurity is greater than 0.1%.

3. Substantially pure desloratadine as claimed in claim 2, wherein the total impurities
are less than 0.3%.

25

4. A substantially pure desloratadine of claim 1, 2 or 3 prepared by a process comprising
acidic hydrolysis of a compound of **formula 3**, where R is selected from COR₁,
COOR₁, wherein R₁ is selected from branched or linear alkyl containing 1 to 6
30 carbon atoms, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and their substituted
analogs; by heating with a strong organic acid or a mineral acid for about 1 hour to
about 24 hours, adjustment of pH of the hydrolysed reaction mixture to a pH

between the range of about 3 to about 5, optional treatment with an adsorbent, adjustment of pH of the reaction mixture to a pH of greater than about 9 and isolation of desloratadine.



5

Formula 3

5. A substantially pure desloratadine of claim 4 prepared by a process comprising acidic hydrolysis of a compound of **formula 3**, by heating with an acid at a temperature between the range of ambient to about 150°C.

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6. A substantially pure desloratadine of claim 4 further comprising recrystallization of desloratadine from a solvent system comprising a mixture of an alcohol and a hydrocarbon solvent.

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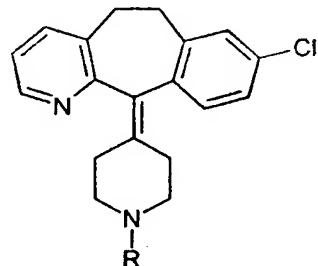
7. A substantially pure desloratadine of claim 6 wherein alcohol is methanol and hydrocarbon solvent is cyclohexane.

20

8. A process for preparation of substantially pure desloratadine comprising acidic hydrolysis of a compound of **formula 3**, where R is selected from COR₁, COOR₁, wherein R₁ is selected from branched or linear alkyl containing 1 to 6 carbon atoms, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and their substituted analogs; and their substituted analogs, by heating with a strong organic acid or a mineral acid for about 25

1 hour to about 24 hours, adjustment of pH of the hydrolysed reaction mixture to a pH between the range of about 3 to about 5, optional treatment with an adsorbent, adjustment of pH of the reaction mixture to a pH of greater than about 9 and isolation of desloratadine.

5



Formula 3

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9. A process as claimed in claim 8 wherein R is COOR₁ and R₁ is ethyl and the organic acid is methanesulfonic acid.

15

10. A process as claimed in claim 8 wherein R is COOR₁ and R₁ is ethyl and the mineral acid is sulphuric acid.

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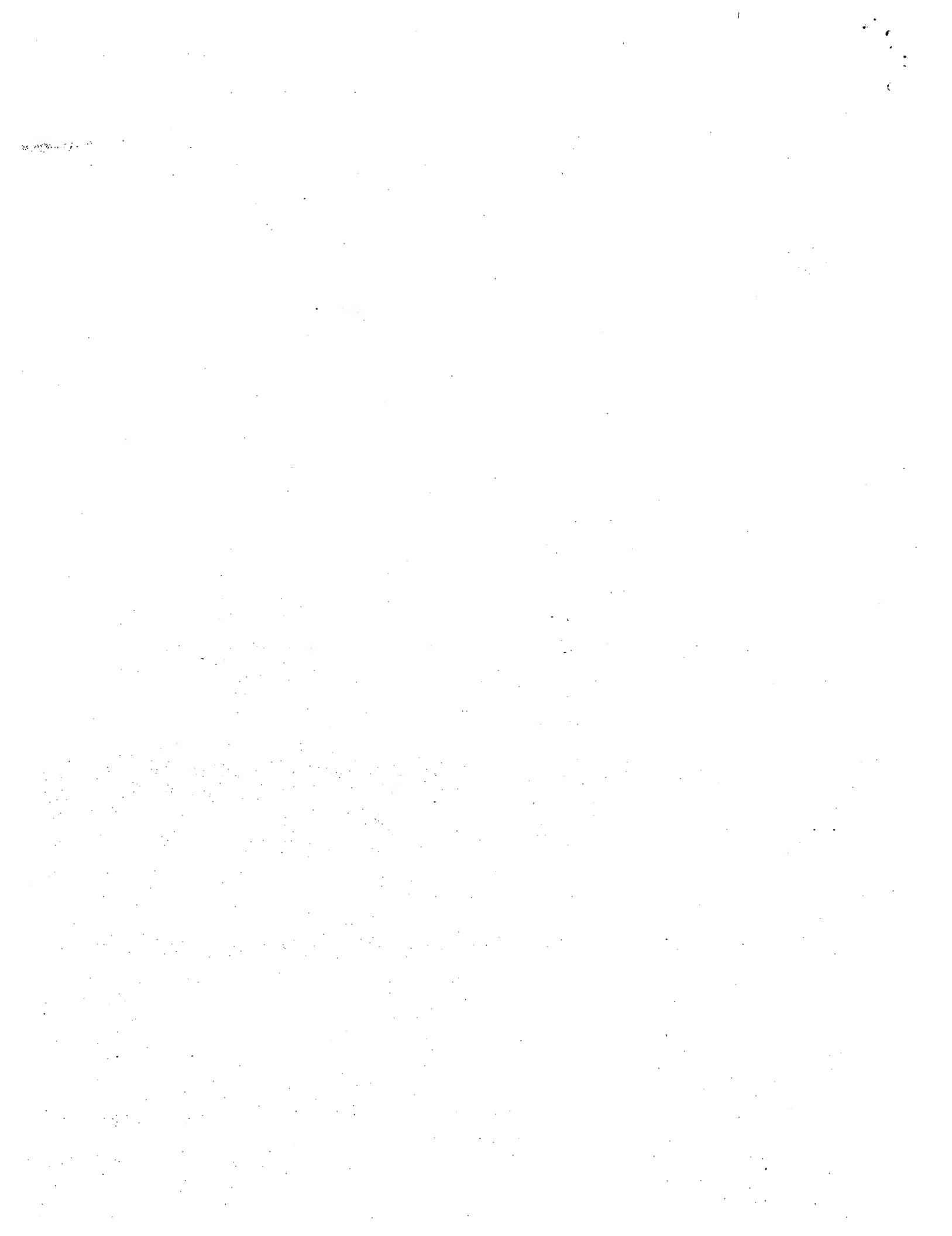
11. A process as claimed in claim 8, comprising acidic hydrolysis of a compound of formula 3, by heating with an acid at a temperature between the range of ambient to about 150°C.

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12. A process as claimed in claim 11, comprising acidic hydrolysis of a compound of formula 3, by heating with an acid at a temperature between the range of about 60°C to about 110°C.

13. A process as claimed in claim 9, wherein the acidic hydrolysis is carried out by heating with metahnesulfonic acid for 5 to 15 hours at a temperature between the range of about 90°C to about 120°C.
- 5 14. A process as claimed in claim 10, wherein the acidic hydrolysis is carried out by heating with sulphuric acid for 1 to 5 hours at a temperature between the range of about 90°C to about 120°C.
- 10 15. A process as claimed in claim 8, wherein adsorbent is selected from charcoal, neutral or alkaline alumina, silica or fuller's earth.
- 15 16. A process as claimed in claim 8, comprising adjustment of pH of the reaction mixture to a pH between the range of about 4 to about 5, treatment with charcoal, adjustment of pH of the reaction mixture to a pH of about greater than 9 and isolation of desloratadine.
- 20 17. A process as claimed in claim 8, further comprising recrystallization of desloratadine from a solvent system comprising of two or more protic or aprotic solvents selected from water, alcohols, linear branched or cyclic hydrocarbons, aromatic hydrocarbons, ethers, ketones, nitriles, esters, and their halo or substituted analogs and the like.
- 25 18. A process as claimed in claim 8, further comprising recrystallization of desloratadine from a solvent system comprising a mixture of an alcohol and a hydrocarbon solvent.
19. A process as claimed in claim 18 wherein alcohol is methanol and hydrocarbon solvent is cyclohexane.
- 30 20. A process as claimed in claim 19, wherein the ratio of methanol:cyclohexane is 1:14 v/v.

21. A process as claimed in claim 8 for preparation of substantially pure desloratadine as described in claim 1, 2 or 3.



(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 2003/086275 A3

(51) International Patent Classification⁷: C07D 401/04, A61K 31/435

(21) International Application Number: PCT/IN2003/000156

(22) International Filing Date: 16 April 2003 (16.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 348/MUM/2002 15 April 2002 (15.04.2002) IN

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

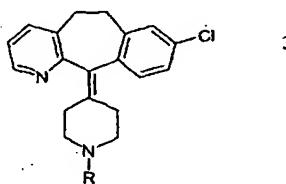
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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- as to the identity of the inventor (Rule 4.17(i)) for all designations
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[Continued on next page]

(54) Title: PREPARATION OF DESLORATATINE



WO 2003/086275 A3

(57) Abstract: The present invention provides substantially pure desloratadine having an HPLC purity greater than 99.5% and having an absorbance less than 0.15 Au at 420 nm for a 5%w/v solution in methanol, which does not show a peak for an impurity at a relative retention time in the range from about 0.85 to about 0.99 (relative to desloratadine appearing at a retention time of 25±5 minutes), which is greater than the discard limit set at less than 0.025% of the total area, when tested according to an HPLC method performed using a Hypersil BDS C₈ column (15cm x 4.6mm, 5 μm particle size) with the following parameters: Mobile phase: Buffer solution having a pH of about 3, methanol and acetonitrile in a volume ratio of 8:1:1; Injection volume: 20μl; Flow rate: 1.5 ml/minute; Run time: 75 minutes; Discard limit: Set at less than 0.025% of total area. The present invention also provides a process for the preparation of substantially pure desloratadine by the process comprising acidic hydrolysis of a compound of formula (3) where R is selected from COR₁, COOR₁ wherein R₁ is selected from branched or linear alkyl (1-6 C), cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and their substituted analogs; and their substituted analogs with a strong organic acid or a mineral acid.



— *patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

(88) Date of publication of the international search report:
12 February 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00156-0

CLASSIFICATION OF SUBJECT MATTER

IPC⁷: C07D 401/04, A61K 31/435According to International Patent Classification (IPC) or to both national classification and IPC
B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: C07D 401/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE: WPI, EPODOC, PAJ, NPL, MEDLINE and XPESP databases; STN Karlsruhe:
CAS: REGISTRY and CA databases

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 85/03707 A1 (SCHERING CORPORATION) 29 August 1985 (29.08.85) cited in the application <i>claim 1, examples.</i>	1-7
X	WO 99/01450 A1 (SCHERING CORPORATION) 14 January 1999 (14.01.99) cited in the application <i>examples.</i>	1-7
A	WO 02/42290 A1 (RICHTER GEDEON VEGYESZETI GYAR RT) 20 May 1935 (20.05.35) 02 cited in the application <i>page 2,3.</i>	8

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Date of the actual completion of the international search
17 October 2003 (17.10.2003)Date of mailing of the international search report
20 November 2003 (20.11.2003)Name and mailing address of the ISA/AT
Austrian Patent Office
Dresdner Straße 87, A-1200 Vienna
Facsimile No. 1/53424/535Authorized officer
SLABY S.
Telephone No. 1/53424/348

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IN 03/00156-0

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